the Examiner's opinion that determining whether a given disease responds or does not respond to CRF antagonism will involve undue experimentation.

The Examiner again presented in support of his opinion the hypothetical scenario wherein a CRF antagonist called "X" is administered to a patient having a particular disease "D", however the patient does not respond to the antagonist "X". The Examiner stated that in such a situation it remains unclear whether or not disease "D" falls within the scope of applicant's claims. In that regard, the Examiner stated that a) "it may be that the next patient will respond" and "it is quite common for pharmaceuticals to work only with some people, not all", b) "it may be that the wrong dosage or dosage regimen was employed", and c) "it may be that 'X' is simply not potent enough for 'D', but that another antagonist 'Y' is potent enough".

Applicant continues to traverse the aforementioned rejection. As indicated in applicant's previous Amendment dated July 7, 1998, whether or not a particular disease or condition can be treated by antagonizing CRF can be ascertained by establishing a connection between antagonizing CRF and treating the disease or condition by suitable experiments on animals, in some cases humans. Of course, as also previously noted, sufficient evidence, such as an adequate number of tests on an adequate number of subjects to actually establish whether or not a given disease responds to CRF antagonism, must be present. However, contrary to the Examiner's analysis of how to determine claim scope, such evidence has already been obtained by scientists in the art and need not necessarily be performed by any single individual or group contemplating whether a particular activity would fall within the scope of applicant's claims. Numerous references in the art, some of which have been discussed in applicant's previous July 7, 1999 Amendment, describe a nexus between CRF antagonism and various disorders and conditions. Thus, the evidence to interpret the scope of applicant's claims has already been collected and documented in the literature. Moreover, as scientists continue to research the contributing factors involved in various disorders and conditions, additional disorders and conditions will be documented as falling within the category of those that can be treated by antagonizing CRF. Applicant submits that one of ordinary skill in the art will thus easily be able to ascertain the scope of the claim language "a disorder the treatment of which can be effected or facilitated by antagonizing CRF" without undue experimentation.

Moreover, the U.S. Patent Office has already issued patent claims using this same type of language. For example, U.S. Patent 5,852,031, issued December 22, 1998 to Desai *et al.*, contains a claim directed to "a pharmaceutical composition for treating or preventing a disease

or condition, the treatment or prevention of which can be effected or facilitated by altering dopamine mediated neurotransmission". Also, U.S. Patent 5,597,826, issued January 28, 1997 to Howard *et al.*, contains claims to a pharmaceutical composition and method for "treating or preventing disorders arising from deficient or excessive serotonergic neurotransmission". As another example, U.S. Patent 5,710,168, issued January 20, 1998 to Chenard, contains claims directed to "a method of treatment of a disease or condition in a mammal, said disease or condition being susceptible to treatment by blocking of NMDA receptor sites". The issuance of U.S. patents containing such claims indicates that the type of claim language at issue is not vague, contrary to the Examiner's view. Copies of the aforementioned references are submitted herewith and also listed on the citation form accompanying this response.

In the March 26, 1999 Office Action, the Examiner also again rejected the claims under 35 USC 112, first and second paragraphs, based on the use of the term "psychosocial dwarfism". The Examiner stated that the term "psychosocial dwarfism" is indefinite. The Examiner further indicated that providing dictionary definitions of the words "psychosocial" and "dwarfism" does not establish that the term itself is definite. The Examiner stated that applicant has presented no evidence that psychosocial dwarfism is a defined medical condition, distinguishable from other types of dwarfism.

In response, applicant submits herewith two examples of references that indicate that psychosocial dwarfism is a defined condition known to those of ordinary skill in the art. The first reference, Albanese *et al.*, indicates that reversibility of growth hormone insufficiency with a change of environment is characteristic of psychosocial dwarfism. The second reference, Bowden and Hopwood, indicates that psychosocial dwarfism is a syndrome caused by deprivation, emotional stress and/or neglect, occurring in both infants and children. Thus, applicant maintains that psychosocial dwarfism is an acceptable term known in the art to indicate a specific condition, and applicant respectfully requests that the Examiner reconsider and withdraw the aforementioned rejection.

The Examiner also maintained that replacement of the term "thioalkyl" with "alkylthio" is clearly new matter. The Examiner maintained that there is no way of telling whether "alkylthio" or "mercaptoalkyl" is what was originally intended by "thioalkyl".

Applicant traverses, for the reasons provided in the July 7, 1998 Amendment, and because applicant believes that it is clear from the context of the term "thioalkyl" in the originally-filed specification that "alkylthio" was intended. Therefore, replacement of the term

"thioalkyl" with "alkylthio" does not constitute new matter. "Thioalkyl" is recited in the original specification as "C_1-C_3 thioalkyl" in a list of possible substituents on a (C_1-C_4) alkyl or (C_1-C_6) alkyl moiety (see, for example, page 4, lines10-18, of the specification). None of the other substituents in the list comprise an alkyl attached directly to the (C_1-C_4) alkyl or (C_1-C_6) alkyl moiety. If applicant had intended mercapto(C_1-C_3 alkyl), then applicant would simply have incorporated such group into the (C_1-C_4) alkyl and (C_1-C_6) alkyl moieties, *i.e.* as mercapto(C_1-C_7 alkyl) and mercapto(C_1-C_9 alkyl). Moreover, also recited in the list of possible substituents on the C_1-C_4 and C_1-C_6 alkyl moieties is "C_1-C_3 alkoxy", which suggests that "C_1-C_3 thioalkyl" actually was meant to indicate a C_1-C_3 alkylthio group, since a C_1-C_3 alkylthio group is analogous to a C_1-C_3 alkoxy group. Thus, applicant maintains that it is clear from the originally-filed specification that "C_1-C_3 alkylthio" was intended, not mercapto(C_1-C_3 alkyl).

The Examiner also asserted in the March 26, 1999 Office Action that the optionally substituted pyrimidyl choice for R^5 lacks enablement. The Examiner stated that this term did not exist in the specification's definition of R^5 as originally filed. The Examiner asserted that the information on page 9, lines 9-15, of the specification, which applicant had pointed out in the July 7, 1998 Amendment, is broader than that inserted by applicant into claim 18 and in the specification by the July 7, 1998 Amendment. The Examiner stated that the information on page 9 is limited to two substituents, not up to four, and that the substituents are drawn from a smaller list of possibilities. The Examiner asserted that additionally the subject matter on page 9 is limited in that it has a narrower definition for R^3 and for the other variables such as R^4. The Examiner further asserted that the material which is described lacks enablement in that it is not covered by the "utility umbrella" since the utility is tied to the compounds of formulas I, II, and III.

Applicant respectfully traverses. The exclusion of pyrimidyl from claim 1 in the originally-filed application and from the "Summary of the Invention" spanning pages 1-5 was clearly an inadvertent error. The Examiner has ignored the language in the specification which applicant noted in the July 7, 1998 Amendment, specifically that the subgenus of compounds of formula I, II and III described on page 9, lines 9-15, was indicated in the original specification to delineate "other more specific embodiments of the invention". If the more specific embodiments can include pyrimidyl as a possibility for R^5, then it makes sense that the genus corresponding to the broadest genus defining the invention also includes pyrimidyl as an option for R^5. Nonetheless, in response to the Examiner's rejection, applicant has amended claim 18

above to, instead of simply pyrimidyl, recite that R^5 can further be pyrimidyl which is substituted with more than two substituents (two or three substituents) independently selected from C_1-C_4 alkyl, -O(C_1-C_4 alkyl), CF_3, OCF_3, -CHO, (C_1-C_4 alkyl)-OH, CN, Cl, F, Br, I and NO_2, wherein said (C_1-C_4) alkyl groups may optionally contain one double or triple bond. This language corresponds identically to the language for pyrimidyl on page 9, lines 12-15, and thus there is clearly support in the originally-filed specification for such compounds as being compounds of the invention. Applicant has also by the above amendments removed (C_1-C_4 alkyl)-O-(C_1-C_4 alkyl), OCF_3, and fluoro as possible substituents on R^5 groups other than phenyl, pyridyl and pyrimidyl, to correspond identically to the language on page 9, lines 9-15, of the originally filed application. There is thus clearly support for the compounds encompassed by amended claim 18 in the originally-filed application. Since such compounds are "more specific embodiments of the invention", they are clearly compounds of the invention and therefore also furthermore have ascribed to them utility as CRF antagonists described in the application.

The Examiner further remarked with respect to R^5 that the addition of CF_3 as a possibility for R^5 is improper. The Examiner asserted that, for example, page 9 of the specification does not provide for a compound with R^3 being CN and R^4 being CF_3, but that amended claim 18 does so provide. It appears that the Examiner meant to object to addition via the July 7, 1998 Amendment of "trifluoromethyl" to the possibilities for R^4. Applicant traverses. The language on page 9, lines 9-15, does not require that each of the more specific possibilities for R^3, R^4, G, and R^5 occur simultaneously on any given compound. Rather, the language suggests that each list of more specific possibilities defines an independent subgenus of compounds of formulas I, II, and III. It is clear from such language that, for example, a compound of formula I could have R^4 being trifluoromethyl and R^3 being CN. Accordingly, applicant maintains that inclusion of trifluoromethyl in claim 18 as an option for R^4 is not unsupported by the original specification and respectfully requests that the Examiner reconsider and withdraw such rejection.

The Examiner also rejected claim 18 on the basis of the additions via the July 7, 1998 Amendment of the choices (C_1-C_4 alkyl)-O-(C_1-C_4 alkyl), OCF_3, and fluoro for group R^{12}. However, as discussed above, these terms have been deleted from claim 18 as possible substituents for all R^5 groups other than phenyl, pyridyl, and pyrimidyl. Support for the latter

can be found in the originally-filed specification, at, for example, page 9, lines 9-15. Accordingly, applicant respectfully requests that this rejection be withdrawn.

The Examiner furthermore asserted that the provision for the optional multiple bond for R^5 inserted by the July 7, 1998 Amendment into claim 18 lacks enablement and description. The Examiner stated that the text on page 14, lines 3-5, of the specification, which applicant had previously noted, does not cover R^5. In response, to advance prosecution and without conceding to the Examiner's belief that such groups are necessarily not enabled by the original disclosure, applicant has removed the language indicating that all of the alkyl groups in R^5 can optionally comprise a double or triple bond. However, applicant has included such language for the R^5 groups phenyl, pyridyl, and pyrimidyl having two or three substituents, since support for such groups can be found in the original specification at page 9, lines 9-15.

In the March 26, 1999 Office Action, the Examiner further asserted that the inclusion of "inflammatory diseases" into the claims constitutes new matter. According to the Examiner, page 1, lines 29-34, refers to the prior art and does not indicate that the claimed compounds are effective for inflammatory diseases. The Examiner also asserted that the aforementioned text on page 1 relates only to stress-related illnesses and thus only to stress-related inflammatory diseases. Therefore, the Examiner concluded, the term "inflammatory diseases" in general in the claims is too broad. The Examiner further asserts that the inclusion of "inflammatory diseases" in the claims renders the terms "rheumatoid arthritis" and "osteoarthritis" superfluous, since these terms are, according to the Examiner's own words (at least with respect to rheumatoid arthritis), inflammatory diseases (the Examiner stated on page 7 of the office action that the term following "inflammatory diseases", which is "rheumatoid arthritis", is an inflammatory disease).

Applicant traverses this rejection. With respect to the Examiner asserting that it is improper to include "superfluous" terms within the claim, applicant does not necessarily agree that the inclusion of terms of varying and overlapping scope within a single claim is improper; however, applicant can easily satisfy the Examiner by adding dependent claims reciting the narrower terms "rheumatoid arthritis" and "osteoarthritis" and canceling said terms from the claim at issue. Applicant will be glad to do so upon indication of otherwise allowable subject matter.

Applicant furthermore maintains that "inflammatory disease" is not new matter. Support for such term in the original specification was explained in applicant's July 7, 1998

Amendment. In particular, applicant would like to point out that the original claim language included the term "inflammatory disorders". This term ("inflammatory disorders") was included within the claims within the phrase "inflammatory disorders such as rheumatoid arthritis and osteoarthritis". Moreover, the specification discusses in the "background" section that CRF antagonists are effective in treatment of inflammatory diseases. Thus, it is clear from the original specification that the phrase "inflammatory disorders such as rheumatoid arthritis and osteoarthritis" was meant to indicate inflammatory disorders, i.e. inflammatory diseases, generally. If it would assist in rendering the subject application allowable, applicant would change the term "inflammatory disease" in the claims to "inflammatory disorder".

The Examiner also maintained that an HIV infection is not a disorder. The Examiner stated that an HIV infection needs its own category. According to the Examiner a disorder is a "disturbance in the regular and natural functions of either body or mind" and "an infection is not part of the regular and natural functions of either body or mind and hence it is not a disturbance in it". In the Examiner's opinion, a fever is a disorder, however an infection is not a disorder. A bee sting, according to the Examiner, is not a disorder. Applicant traverses; applicant maintains that an infection is a disturbance in the regular and natural functions of either body or mind. An infection is not part of the regular functioning of the body, and therefore an infection is a disorder. Nonetheless, if the Examiner could suggest to applicant some language modifying the claims, albeit not at a substantive level, that he considers appropriate for categorizing an HIV infection, applicant would be happy to consider amending the claims in such a manner. Applicant also has amended claims 23 and 24 hereinabove to include the word "virus" in the phrase "human immunodeficiency virus infections", which word was inadvertently omitted from said claims in the July 7, 1998 Amendment. Applicant maintains that there is support for the term "human immunodeficiency virus infections" in claims 23 and 24, since the term is recited in the originally-filed application as being treatable by compounds of the formula and having the groups set forth in claim 25.

The Examiner also asserted that claim 22 lacks description and is unclear. Applicant added claim 22 in the July 7, 1998 Amendment to provide a claim having the same scope as claim 18, but for the text added to claim 18 that was discussed above. For clarity, applicant has above cancelled claim 22 and added claim 25. Claim 25 is in independent form and is directed to a genus the same as claim 18, except for that it does not include pyrimidyl for R^5, trifluoromethyl for R^4, or (C_1-C_4 alkyl)-O-(C_1-C_4 alkyl), OCF_3, or fluoro for R^{12}. Support for

claim 25 can be found in the originally-filed application, for example in originally-filed claim 1. Applicant has also amended claims 23 and 24 so that they depend from claim 25 rather than cancelled claim 22.

The Examiner maintained that claims 2-4, 8-10, 12-14, 18, and 30-24 are drawn to an improper Markush group. The Examiner stated that limiting the claims to pyrrolopyrimidines would overcome this rejection. The Examiner stated that this rejection is maintained for the reasons set forth in the July 25, 1997 Office Action, and applicant notes that said reasons included that such unrestricted claims, in the Examiner's view, "embrace multiple inventions". In response, applicant has therefore restricted the claims of the subject application to pyrrolopyrimidines. Applicant reserves the right to prosecute the cancelled subject matter, which is considered by the Patent Office to be directed to a different invention than the pyrrolopyrimidines, in one or more patent applications filed in the future.

The Examiner rejected claim 20, 21, 23, and 24 under 35 USC 112, first paragraph, asserting that the scope of these claims is not enabled. The Examiner argued that no medicinal known to man has been capable of treating the number of disorders recited in said claims. The Examiner further stated that to get a single compound, let alone a genus, to be effective against such a number of disorders has been beyond the reach of medicine. The Examiner argued that the "failure to achieve such a goal" places the burden on applicants to show that their compounds really can accomplish such a goal. The Examiner cited In re Ferens, 163 USPQ 609.

Applicant traverses. First, it is not true that the failure to achieve a particular goal in treating a disorder or disorders places the burden on applicants to show that their compounds can achieve the goal. The very case, In re Ferens, which the Examiner has cited says just the opposite. In In re Ferens, the Court stated, "[o]f course, we recognize that the fact that some result has not previously been achieved is no reason for rejecting an application purporting to disclose how to achieve that result, since the very purpose of the patent system is to encourage attainment of previously unachievable results" (163 USPQ at 611). Moreover, in the analysis of the patent law made by the Patent Office in connection with preparing the Utility Guidelines in the M.P.E.P. (copy attached), it is stated that the mere fact that there is no known cure for a disease should not serve as the basis of an Examiner's conclusion that such an invention lacks utility, rather the Examiner should only reject the claims if he or she can establish a *prima facie* case that the asserted utility is not credible. Thus, a claim to treating a certain disorder or

disorders can still be deemed credible, even if the particular disorder or disorders have not yet been treatable.

Applicant further maintains that it is not so incredible to be able to treat numerous disorders with a particular compound or genus of compounds having a certain activity, in the instant case CRF antagonizing activity. Just because a single compound, for example fluoxetine (PROZAC), a selective serotonin reuptake inhibitor, is marketed for depression, does not mean that fluoxetine could not be used to treat numerous disorders. U.S. Patents 5,795,895; 5,776,969; 5,744,501; and 5,223,540 indicate that SSRIs can also be used to treat anorexia, sleep disorders, late luteal phase dysphoric disorder, and anxiety/mood disorder, respectively. A particular neurotransmitter or hormone can have extensive systematic effects, as discussed in applicant's previous Amendment and supported by references such as Stratakis and Chrousos and Chalmers *et al.*, and thus it is not incredible that a single genus of compounds would be able to treat a number of disorders, including the number of disorders recited in applicant's claims.

With respect to In re Citron, 139 USPQ 520, applicant maintains that In re Citron does not represent a bar to the number of disorders an applicant can claim to be able to treat without having that claim be considered incredible. Rather, the court in In re Citron objected to the nature of the disorders claimed to be treatable, the treatments of which at the time (1964) were not known to be attainable (139 USP 520, 521). Also, in In re Citron, the chemical nature of the ingredient (the acetone soluble extract of the fat soluble components in cancer tissue) of the composition being claimed was unknown (139 USPQ 520, 521).

In light of the above, and for the reasons previously presented by applicant, applicant respectfully requests that the Examiner reconsider and withdraw the aforementioned rejection.

The Examiner furthermore specifically rejected the aforementioned claims since they are directed, in part, to treatment of cancer. The Examiner stated that the claims set forth the treatment of cancer generally, but that there never has been a compound capable of treating cancer generally. The Examiner asserted that although there are compounds that treat a range of cancers, no one has ever been able to figure out how to get a compound to be effective against cancer generally or even a majority of cancers. The Examiner asserted that even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers. The Examiner concluded that, despite the existence of chemotherapeutic agents that destroy malignant cells without substantially interfering with the growth of normal

cells, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The Examiner would apparently like for applicant to take his word for each of the aforementioned statements, unsupported by evidence. This is improper. Applicant does not concede that each of the aforementioned statements is true. It is recognized by those of ordinary skill in the art that stress can be a contributing factor in cancer and that combating stress can therefore reduce the likelihood of cancer formation and propagation. This is supported by Fackelmann and Raloff, which was submitted with and referenced in applicant's July 7, 1998 Amendment. In further support thereof, applicant submits herewith U.S. Patent 5,464,872 (hereinafter, Langlois *et al.*), which indicates that pathologies in which melatonin is involved include "cancer" and "stress" (see column 7, lines 43-47). Langlois *et al.* further indicates that compounds described as having a high affinity for melatonin receptors can be used in treating disorder of the melatonergic system (see, for example, the abstract of Langlois *et al.*). Thus, the teachings of Langlois *et al.* (in addition to the teachings of Fackelmann and Raloff) contradict the Examiner's assertion that it is incredible to treat cancer generally; the aforementioned references indicate that cancer can be generally treated. Applicant also submits herewith a copy of WO 99/11643 which recites a genus of compounds indicated to have CRF receptor binding activity, thereby altering the anxiogenic effects of CRF secretion; the compounds are indicated as useful in treating anxiety-related disorders (see page 7, lines 20-33). WO 99/11643 thus supports a connection between CRF secretion and stress. Since CRF antagonism is indicated in the art as useful in treating stress-related illnesses, and since it is also indicated in the art that stress contributes to cancer, applicant submits that a showing of CRF antagonism as in the present specification adequately enables the use of the claimed compounds for treating cancer. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the aforementioned rejection.

The Examiner also indicated that specifically treatment of "chemical dependencies and addictions" is not enabled on the asserted basis that such treatment is incredible. To quote the Examiner:

> "The notion that a compound could be effective against chemical dependencies in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for 'drug addiction' generally". (Emphasis added).

Applicant traverses. That there probably never will be a treatment for drug addiction is purely speculation on the Examiner's part, and such speculation is improper. The Examiner has provided no evidence supporting the aforementioned allegations. In contrast, applicant has provided evidence, in the July 7, 1998 Amendment, to the contrary. Applicant provided the information on REVIA, useful for treating alcohol dependence and for blocking the effects of exogenously administered opioids. The Examiner asserted that all attempts to find a pharmaceutical to treat chemical addictions generally have failed because different harmful chemicals, *e.g.* nicotine and cocaine, bind to different receptors in the CNS. This is not true, because REVIA is indicated to be useful against both alcohol addiction and opioid dependance. Although REVIA binds to opiate receptors and thus can treat opioid addiction, it also is able to treat alcohol addiction. Also, as discussed in the July 7, 1998 Amendment, Stratakis and Chrousos indicate that chronic activation of the hypothalamic-pituitary-adrenal axis, which is regulated by CRF, has been shown also in chronic active alcoholism and alcohol and narcotic withdrawal. Moreover, a single drug could, contrary to the Examiner's assertion, treat drug addiction; the compound does not necessarily have to interact with the particular receptor or receptors to which the harmful drug binds in order to have activity in reducing the addictive behavior. For example, Ciccocioppo, "The role of serotonin in craving: from basic research to human studies", Alcohol and Alcoholism, Mar-Apr 1999, 34(2), pp. 244-253, submitted herewith, indicates that increasing evidence suggests that craving may play a central role in the mechanisms of addiction; it is proposed that 5-hydroxytryptamine (5-HT) deficiency may contribute to the loss of control over drug-taking, which is a crucial factor for the maintenance of addictive behavior. Thus, compounds, such as selective serotonin reuptake inhibitors, that increase serotonin availability, may assist in treating drug addictions in general.

The Examiner noted that TRANXENE is a standard benzodiazepine antianxiety drug. The Examiner asked why a CRF antagonist should be expected to do what a benzodiazepine antagonist can do. The answer to this question is irrelevant to the argument the Examiner is attempting to make that treating drug addiction in general is incredible. Treating drug addictions in general is not so incredible as to warrant extra proof on applicant's part, and the existence of drugs such as TRANXENE and REVIA, as well as other evidence, such as that presented in Ciccocioppo, attests to this. In light of the above, applicant respectfully requests that the Examiner again reconsider and withdraw the rejection of the claims based on inclusion

of treatment of chemical dependencies and addictions and drug and alcohol withdrawal symptoms.

In sum, the Examiner is categorizing the treatment of certain disorders, such as chemical dependencies and addictions, as being incredible when they are not and is therefore placing too high of a burden on applicant for obtaining a patent.

The Examiner further specifically rejected the claims based on inclusion of treating human immunodeficiency virus infections. The Examiner stated that all successful treatments of AIDS have involved antiviral agents. According to the Examiner, "no one has ever been able to get other attempts to work". The Examiner concluded that this demonstrates that the level of skill in this art is not high enough to get other methods (other than antiviral methods) to work.

Applicant respectfully traverses. Again, the Examiner is inappropriately characterizing the treatment of a disorder, in this case treatment of HIV infection with a substance other than an antiviral substance, as being incredible. Contrary to the Examiner's assertion, HIV infection is indeed treatable by substances that are not necessarily antiviral agents. In fact, HIV infection is indicated to be treatable by immune-boosting substances. In support of this, applicant submits herewith Zou *et al.*, "Acute upregulation of CCR-5 expression by CD4+ T lymphocytes in HIV-infected patients treated with interleukin-2." AIDS, 13(4), pp.455-63 (March 11, 1999). Zou *et al.* indicates that the cytokine interleukin-2 promotes immune reconstitution and can be used to treat HIV-infected patients. Also, Kinchington, "Recent Advances in Antiviral Therapy", J.Clin. Pathol. 52:89-94 (1999) suggests that immunomodulators, including cytokines and small molecular weight molecules, may assist in treating HIV infection (see Kinchington, submitted herewith, page 99, second column, last sentence). As noted in applicant's July 7, 1998 Amendment, Owens and Nemeroff suggests a connection between CRF antagonism and the immune system. Other references cited by already cited by applicant indicate that CRF can compromise the immune system and that therefore CRF antagonists would be helpful in bolstering the immune system. Abreu *et al.*, for example, indicates that intracerebroventricular injection of CRF compromises immune function (Column 1, lines 35-53). Stratakis and Chrousos also states that "[s]tress-associated CRH hypersecretion, and the resultant glucocorticoid-, catecholamine-, and IL6-mediated immunosuppresion correlate well with such clinical observations as the suppression of the immune and inflammatory reaction during chronic psychological and physical stress, the reactivation of autoimmune diseases during the

postpartum period or following cure of Cushing's syndrome(CS), and the decreased ability of the stressed organism to fight viral infections and neoplasms," (see page 206, second column).

Thus, applicant contends that one of ordinary skill in the art would not find it incredible to treat HIV infection with a substance having activity other than antiviral activity, such as immune function-enhancing activity. Applicant has enabled CRF antagonizing activity for the claimed invention in the specification. Since it is indicated in references in the art that CRF antagonism enhances immune functioning, one of ordinary skill would likewise be able to enhance immune function and thereby treat HIV infection using applicant's claimed compounds. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the aforementioned rejection.

The Examiner in the March 26, 1999 Office Action also rejected the claims based on the inclusion specifically of Alzheimer's disease. The Examiner's rejection in part is based on the belief that a treatment for Alzheimer's disease is so incredible that it warrants further evidence of applicability than normally required for a pharmaceutical treatment claim. This is the same basis asserted by the Examiner against applicant's claim for treating drug addiction. Applicant does not necessarily agree that treating Alzheimer's disease should be considered incredible. An interpretation of the court cases pertaining to whether a utility is "incredible" or not reveals that only in those situations where treating a particular disorder had not ever been realized, despite years of research, was a claim to treating the disorder considered incredible (see, *e.g.*, Ex parte Stevens, 16 USPQ2d 1379, which applicant cited in the July 7, 1998 Amendment; the utility in Ex parte Stevens was treating cancer). In such situations, a question is raised as to whether it might be impossible to treat the disorder at all. However, in the instant case, even the Examiner has agreed that treatments for Alzheimer's disease have been made; the Examiner stated in the March 26, 1999 Office Action that "[d]espite extraordinary efforts with a variety of agents in this area, only two pharmaceuticals have been made to work, both acetylcholinesterase antagonists, a property that these compounds are not disclosed to have," (emphasis added). Moreover, that the presently claimed compounds may not have acetylcholinesterase antagonizing action is irrelevant to the determination of whether a claim to treating Alzheimer's disease should be considered incredible. It should not, because the state of the art is that Alzheimer's disease can be treated; whether or not Alzheimer's disease can be treated is no longer a question that needs to be answered.

The Examiner also relied on Chalmers *et al.* to reject the claims due to the recitation of Alzheimer's disease on the grounds that Alzheimer's disease is indicated to be associated with low levels of CRH. In response, applicant has deleted Alzheimer's disease from the claims. Applicant reserves the right to prosecute a claim to such an invention in one or more patent applications filed in the future.

The Examiner also rejected the claims due to the inclusion specifically of treating obesity. The Examiner again relied on Chalmers *et al.* for indicating that obesity is associated with low levels of CRH to support this rejection. In response, applicant has removed obesity from the claims. Applicant, however, reserves the right to file one or more patent applications containing a claim or claims to such an invention in the future.

The Examiner also rejected the claims based upon the specific recitation of atypical depression, fatigue syndrome, and fibromyalgia, and autoimmune disorders. The Examiner relied on Stratakis and Chrousos for indicating that such disorders are associated with low levels of CRH. In response, applicant has deleted these disorders from the claims. Applicant reserves the right to pursue a claim or claims pertaining to the use of the present compounds for treating one or more of the aforementioned disorders in one or more patent applications filed in the future.

The Examiner also rejected the claims of the present application based on the specific recitation of stroke. According to the Examiner, stroke represents one of the most intractable medical challenges. The Examiner stated that even patients who survive stroke normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. The Examiner further stated "cerebrovascular therapy has so far been limited to trying to prevent futher damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction, This is generally done surgically." The Examiner asserted that effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science.

The Examiner again apparently expects applicant to believe his statements without supporting evidence. The Examiner has provided no evidence supporting the aforementioned statements. The basis for the Examiner's rejection amounts again to categorizing the treatment of stroke as not being credible. Applicant traverses. Applicant submits that stroke is not considered something impossible to treat. For example, Kapelle *et al.* (EMBASE abstract), included herewith, indicates several drugs that can be used to treat stroke, specifically,

acetylsalicyclic acid, warfarin, and alteplase. Furthermore, as previously noted by applicant, Chalmers *et al.* indicates that antagonists of CRF receptors can inhibit ischemic and excitotoxic brain damage and thus be useful in treating stroke. Applicant therefore maintains that the present specification is sufficient to enable applicant's claim to treating stroke (as well as pharmaceutical compositions for treating stroke).

Applicant would also like to respond to the Examiner's comments regarding the references applicant has cited. The Examiner stated in the March 26, 1999 Office Action that Owens (Owens and Nemeroff) is and older (1991) reference and cannot supply information about the state of the art at the time of the invention. The Examiner, however[], incongruously relies on Owens for the assertions that "the research necessary to understand basic CRF physiology remains to be done and that "pharmacological agents are only possibilities, not realities". Applicant contends that since the Examiner considers Owens to be unrepresentative of the state of the art, the statements from Owens upon which the Examiner is relying likewise should be considered outdated. Applicant does not necessarily agree with the Examiner's view of Lyons. Applicant maintains that Suemaru and Suda provide support that there is a connection between CRF antagonism and treating hypoglycemia.

In conclusion, applicant maintains that the claims as amended herein are clear and are supported by the originally-filed specification. Accordingly, applicant submits that the claims are in condition for allowance. Applicant respectfully requests the earliest possible notification of allowable subject matter.

If a telephone interview would be of assistance in advancing prosecution of this application, the Examiner is invited to telephone applicant's attorney at the telephone number below.

No fee, other than the $380.00 for the two month extension of time authorized by the Petition filed herewith, is believed necessary for filing this Amendment. However, if an additional fee is found necessary in connection with filing this Amendment, authorization is hereby given to charge such fee to Deposit Account No. 16-1445.

Respectfully submitted,

Date: August 26, 1999

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